A retrospective investigation of advanced periodontal disease as a risk factor for septicemia in hematopoietic stem cell and bone marrow transplant recipients

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Objective. Septicemia is a cause of death in hematopoietic stem cell transplant (HSCT) recipients. Extraction of teeth with advanced periodontitis has been advocated before HSCT to prevent septicemia in myeloablated hosts. The primary aim of the present study was to determine impact of chronic periodontitis, as measured by radiographic alveolar bone loss, on septicemia and transplant mortality.

Study design. A retrospective design was used to study 77 subjects who received pretransplant dental evaluation, panoramic radiography, and full myeloablative allogeneic HSCT to treat hematologic malignancies. Radiographic crestal alveolar bone loss was measured with a Schei ruler on all teeth. Microorganisms isolated from positive blood cultures within the first 100 days after transplant were categorized as of likely origin from periodontal, oral, or any body sites. Spearman correlation and logistic regression analysis assessed associations between positive blood cultures, mean subject whole-mouth percent radiographic crestal alveolar bone loss, and 100-day survival.

Results. Radiographic crestal alveolar bone loss per study subject averaged 13% ± 7%, with 18.2% exhibiting bone loss of 20% or greater. During the initial 100 days after transplant, 63.6% subjects yielded septicemia-associated positive blood cultures, with *Staphylococcus epidermidis, Streptococcus mitis, Enterococcus faecalis, Streptococcus sanguis, Staphylococcus aureus,* and *Escherichia coli* as the most common isolates recovered. No statistically significant associations were found between mean subject radiographic alveolar bone loss and septicemia of likely periodontal or oral origin.

Conclusions. In this preliminary study, no relationship was found between radiographic periodontal status and septicemia or mortality within the initial 100 days after transplant. A larger-sized, prospective study is warranted to further delineate the risk of septicemia from periodontal and other oral diseases in immunocompromised patients.

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There has been a progressive increase in the use and success of hematopoietic stem cell transplant (HSCT) to treat hematologic neoplasms and solid tumors. Optimum transplant management involves appropriate patient selection, thorough pretreatment dental evaluation, prompt management of complications during immunosuppression, and regular post-transplant follow-up. Septicemia occurs frequently during HSCT and can be fatal. Numerous oral microorganisms such as viridans streptococci,[1,2] *Capnocytophaga*,[3,4] *Neisseria* species,[5] and *Fusobacterium nucleatum*[6] can cause septicemia and other complications during cancer therapy. Most notably, viridans streptococci are an increasing cause of septicemia in neutropenic patients with can-

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cer.[1,7] This infection, as well as septicemia from *Stomatococcus mucilaginosus*,[8] can lead to acute respiratory distress syndrome and acute respiratory failure.[9]

The purpose of pre–HSCT dental evaluation is to identify and eradicate chronic and occult infections that might become life threatening during the period of neutropenia after transplant. The National Institutes of Health (NIH) consensus statement on oral complications of cancer therapy[10] recognized that "dental foci" are potential sources of systemic infections that need to be "eliminated or ameliorated" by extraction or endodontic therapy. Currently, teeth with advanced periodontal disease are considered as chronic oral infections that may potentially cause septicemia during neutropenia. This assumption is based on several clinical observations. First, the microbial load in the gingival crevice around the teeth increases with advancing periodontal disease.[11] Second, bacteremia caused by tooth brushing occurs more frequently in patients with severe periodontitis, suggesting that inflamed tissues are more permeable to bacteria.[12] Finally, previous studies on small numbers of cancer patients suggested that inflamed periodontal tissues represent a significant source of potentially pathogenic oral flora that can enter the bloodstream of immunocompromised patients.[13-15]

Currently, there is no conclusive scientifically demonstrated evidence that patients with more advanced periodontal disease are at increased risk for septicemia after HSCT. It is important to assess the risks of periodontal disease and balance them with the effect of pre–HSCT dental extractions on the incidence of septicemia, because extraction of multiple teeth may also compromise nutrition during and after transplantation. In addition, dental treatment options to replace extracted teeth are limited, and patients who develop oral graft-versus-host disease (GVHD) have difficulty wearing partial dentures. To address these issues preliminarily, a retrospective cohort study was conducted to determine whether advanced periodontal disease was a risk factor for the development of septicemia and death during the first 100 days after HSCT.

MATERIAL AND METHODS

Patient selection

The medical and dental records of patients treated between January 1996 and September 1999 by the National Heart, Lung and Blood Institute (NHLBI) of the NIH were reviewed retrospectively. Subject inclusion criteria were (1) a complete dental examination with a panoramic radiograph before HSCT, (2) at least 14 teeth present during HSCT, (3) no symptomatic pulp pathologic condition or teeth with periapical pathologic condition throughout the transplant or the first 100 days after transplant, and (4) full myeloablative transplant. These patients were enrolled in Institutional Review Board (IRB)–approved clinical protocols for transplantation and had signed informed consent documents (12 different protocols across the group). This study was a secondary analysis of clinical data generated during the pretransplant period and the first 100 days after transplantation. For pretransplant conditioning, all patients received cyclophosphamide 120 mg/kg intravenously. In addition, 20 patients received 13.6 Gy total body radiation or busulfan 16 mg/kg by mouth, and 57 patients received fludarabine 125 mg/m^2. Cyclosporine was given post-graft during the first 6 months after transplant. As antibacterial prophylaxis to prevent GVHD, norfloxacin 400 mg by mouth twice per day was started 7 to 10 days before transplantation and continued until neutropenia resolved (1000 neutrophils or greater/mm^3). Acyclovir was given for 100 days after transplantation as prophylaxis against herpes virus infections, and weekly trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis carinii* was started on day 30 after transplant. Intravenous immunoglobulin 0.5 g/kg was given weekly for the first 100 days after transplant in patients receiving total body irradiation or busulfan. The transplant procedure depended on the protocol in which the patient was enrolled, and it involved infusions of either allogeneic bone marrow cells (bone marrow transplant [BMT]) or stem cells harvested from peripheral blood (peripheral blood stem cell transplant [PBSCT]).

Patients

Of 141 patients who received HSCT between January 1996 and September 1999, 59 were excluded from the present study because they received substantially less immunosuppression (nonmyeloablative transplant recipients), 3 for having less than 14 teeth, and 2 because they underwent transplant procedures with teeth that demonstrated radiographic evidence of periapical pathologic condition. The 77 subjects fulfilling inclusion criteria for the present study had a mean age of 37.5 ± 11.9 years, with an age range of 13 to 65 years. A total of 61 of these subjects had hematologic malignancies, with the most common diagnoses being chronic myelogenous leukemia (32), acute myelogenous leukemia (18), and myelodysplastic syndrome (11). Fifty-seven patients received PBSCT, and 20 received BMT.

Sixty-six (85.7%) patients received dental treatment before transplant, which included standard prophylaxis (76.6%), extractions (41.6%), and operative procedures (35.1%). In general, teeth were removed if there was advanced caries, periapical pathologic condition, or poor periodontal prognosis. Eleven of the 32 patients undergoing extractions had only 1 tooth removed, whereas 5 patients had between 6 and 9 teeth extracted.

Blood cultures

Blood samples were drawn from intravenous catheters when patients exhibited clinical signs of septicemia (ie, fever of 37.8°C or greater). A combination of the manual Isolator tube (Warmpole Laboratories, Cranbury, NJ)[16] and automated BacT/Alert (Organon Teknika Corp, Durham, NC)[17,18] blood culture systems were used to optimize recovery of microorganisms from blood, as previously suggested.[19]

Isolator tubes were inoculated with 8 to 10 mL of blood and centrifuged for 30 minutes at 3000 *g*, with concentrates plated onto chocolate agar, horse blood agar, and brain heart infusion agar media. The plates were incubated in 5% CO_2 at 35°C and checked daily for microbial growth for up to 5 days. Approximately 3 to 5 mL of blood also were inoculated each into a set of aerobic and anaerobic BacT/Alert blood culture bottles. The aerobic bottles contained 40 mL of supplemented tryptic soy broth and 0.035% sodium polyanetholesulfonate as an anticoagulant in a CO_2 in air atmosphere, with anaerobic bottles also containing 0.00005% menadione, 0.0005% hemin, and reducing agents in a CO_2 in nitrogen atmosphere. The bottles were placed into a BacT/Alert incubator at 35°C for up to 5 days, which provides automated detection of microbial growth via light reflectance spectrophotometric monitoring of increases in CO_2 concentrations associated with microbial metabolism (producing a pH-related yellow color change in a sensor located at the base of each BacT/Alert bottle). No bacterial culture growth after 5 days of incubation was considered a negative result.[20] The microorganisms in positive blood cultures were identified by using a composite of phenotypic and biochemical reactions.[21,22]

Classification of blood culture pathogens

The results of all positive blood cultures during the first 100 days after transplantation were tabulated (Table I). Isolates were categorized 3 different ways for statistical analyses. If the microorganism typically is isolated frequently from subgingival periodontal sites, on the basis of previously published observations,[11,23] it was classified as an organism of likely periodontal origin (periodontal). If the isolate was a frequent inhabitant of supragingival oral sites,[11] it was considered as an organism of likely oral origin (oral). The third category comprised isolates that are frequently recovered from both oral and nonoral body sites (any site). Organisms such as *Streptococcus mitis* were placed in all 3 categories.

Dental evaluation

The dental examinations were performed 1 to 3 weeks before transplantation to identify potential oral sources of infection, and treatment was given when indicated and if time permitted. Caries and periodontal disease were diagnosed by clinical examination and by panoramic, intraoral periapical, and bite-wing radiographs.

Table I. Microorganisms recovered from blood cultures

Isolated organisms	*No. of culture-positive subjects*	*Origin of septicemia*
Aerobic and facultatively anaerobic Gram-positive bacteria		
Bacillus cereus	1	A
Enterococcus faecalis	7	A
Enterococcus faecium	2	A
Lactococcus lactis	1	A
Micrococcus species	2	O,A
Rhondococcus rubra	1	A
Staphylococcus aureus	3	A
Staphylococcus epidermidis	15	A
Staphylococcus haemolyticus	2	A
Staphylococcus hominis	1	A
Streptococcus adjacens	1	A
Streptococcus mitis	14	P,O,A
Streptococcus mutans	1	P,O,A
Streptococcus pneumoniae	1	A
Streptococcus sanguis	3	P,O,A
Streptococcus species	4	P,O,A
Aerobic and facultatively anaerobic Gram-negative bacteria		
Acinetobacter baumannii	1	A
Acinetobacter lwoffii	1	A
Capnocytophaga species	1	P,O,A
Enterobacter cloacae	1	A
Escherichia coli	3	A
Klebsiella pneumoniae	1	A
Pseudomonas aeruginosa	1	A
Pseudomonas oryzihabitans	1	A
Sphingomonas paucimobilis	2	A
Stenotrophomonas maltophilia	1	A
Anaerobic Gram-positive bacteria		
Gemella morbillorum	1	P,O,A
Gemella species	2	P,O,A
Propionibacterium acnes	1	A
Yeast and fungi		
Candida albicans	1	A
Candida glabrata	1	A
Candida krusei	1	A
Candida parapsilosis	1	A
Cryptococcus albidus	1	A
Trichosporon beigelii	1	A

A, Any site; *O*, likely from sites in oral cavity; *P*, likely from subgingival (periodontal) sites.

Periodontal assessment

Full-mouth periodontal probing depths were infrequently recorded because the patients were often neu-

tropenic or thrombocytopenic. Consequently, the periodontal status was assessed as the percent radiographic crestal alveolar bone loss, which was determined by a single trained radiographic examiner measuring interproximal alveolar bone height from panoramic radiographs by using a modification of the Schei ruler,[24,25] which has been shown to provide excellent detection of radiographic changes in alveolar bone level.[26,27] The greater value of bone loss for the mesial and distal measurements per tooth scored was recorded, and the mean percent radiographic crestal alveolar bone loss per study subject was calculated. Study subjects were categorized into 2 groups by using criteria previously used in other studies to identify clinically significant periodontitis:[28-31] those with no or low amounts of bone loss corresponding to a mean subject percent radiographic crestal alveolar bone loss of less than 20%, and those exhibiting high amounts of bone loss corresponding to a mean percent radiographic crestal alveolar bone loss of 20% or greater.

Statistical analysis

Descriptive statistics, including means and standard deviations (SDs), or counts and percentages were calculated. Continuous variables were compared by t tests or Wilcoxon rank sum test when appropriate and categorical variables by Mantel-Haenszel χ_2 test. Univariate analysis of various parameters was tested with Spearman correlation analysis. Logistic regression analysis used the incidence of septicemia from microorganisms of likely periodontal, oral, or any body site origin as the dependent variable and mean subject percent radiographic crestal alveolar bone loss and age as predictor variables. Logistic regression analysis was also used to assess for significant associations between 100-day survival (dependent variable) and the following predictor variables: mean subject percent crestal alveolar bone loss, septicemia from microorganisms of likely periodontal origin, septicemia from microorganisms of likely oral origin, and age. Data analyses were performed with the SAS statistical software program (SAS Institute Inc, Cary, NC).

RESULTS

At baseline, radiographic crestal alveolar bone loss scored on a mean 22 teeth per subject averaged 13% ± 7%, with a subject range of 2.5% to 34.3% and a range for individual teeth of 0% to 90%. A statistically significant positive relationship was found between mean subject whole-mouth radiographic crestal alveolar bone loss and subject age ($r = 0.52$, $P = .0001$). A total of 14 (18.2%) subjects exhibited mean whole-mouth radiographic crestal alveolar bone loss of 20% or greater,

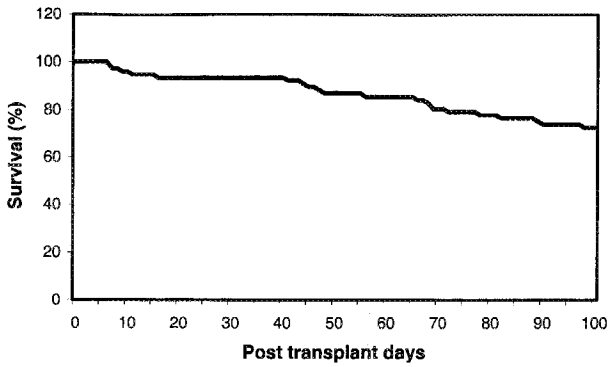

Figure. Survival plot showing percentage of subjects who survived the first 100 days after HSCT.

indicative of a marked degree of destructive periodontal disease.

During the initial 100 days after HSCT therapy, 21 (27.3%) study subjects died, providing a 72.7% survival rate (Figure). A total of 49 (63.6%) study subjects yielded positive blood cultures associated with clinical signs of septicemia during the initial 100 days after HSCT. Among the 81 total isolates recovered from positive blood cultures, 87.7% were aerobic and facultatively anaerobic microorganisms, 7.4% were yeasts and fungi, and 4.9% were anaerobic bacteria. The most common microbial species identified were *Staphylococcus epidermidis* (in 15 subjects), *Streptococcus mitis* (14 subjects), *Enterococcus faecalis* (7 subjects), *Streptococcus sanguis* (3 subjects), *Staphylococcus aureus* (3 subjects), and *Escherichia coli* (3 subjects) (Table I). No Gram-negative anaerobic organisms were isolated from any of the positive blood cultures.

A total of 21 subjects yielded 2 or more microbial species in positive blood cultures, with 9 (42.9%) of these persons dying within the first 100 post–HSCT days. This proportion of deaths was higher, but not statistically significant, than the 21.4% mortality rate found among the 2 subject groups, each composed of 28 subjects, which showed either a single blood culture species or negative blood cultures. Interestingly, all 3 study subjects from whom blood cultures yielded 5 different microbial species died within 100 days after HSCT therapy, suggestive of a higher mortality risk with increasing numbers of microbial species in positive post–HSCT blood cultures.

Among subjects with positive blood cultures, 20 yielded organisms of likely subgingival (periodontal) origin, 23 with organisms of likely origin from the oral cavity, and 49 with organisms likely originating from any body sites. Table II presents the distribution of blood culture findings by their likely sources of body site origin among study subjects exhibiting mean ra-

Table II. Relationship between baseline radiographic crestal alveolar bone loss and likely sources of septicemia after HSCT

Mean subject whole-mouth radiographic bone loss	Septicemia of likely periodontal origin (P = .134)		Septicemia of likely oral origin (P = .09)		Septicemia of any origin (P = .07)	
	Present	Absent	Present	Absent	Present	Absent
≥20%	2*	12	2	12	6	8
<20%	18	45	21	42	43	20

*No. of study subjects.

diographic crestal alveolar bone loss of either 20% or greater or less than 20% at baseline. With each of the 3 postulated sources of post–HSCT septicemia origin as the dependent variable in separate logistic regression analyses, no statistically significant association was found for mean subject percent radiographic crestal alveolar bone loss as an explanatory variable while controlling for subject age (data not shown). Similarly, no statistically significant associations between post-HSCT septicemias of various body site origins and baseline radiographic values were found when subject age was not adjusted for ($P = .134$ for septicemia of likely periodontal origin, $P = .090$ for septicemia of likely oral cavity origin, and $P = .070$ for septicemia of any body site origin; Mantel-Haenszel χ_2 test) (Table II). Logistic regression modeling with subject survival as the dependent variable found no statistically significant associations for mean subject percent radiographic crestal alveolar bone loss or septicemia of likely periodontal or oral cavity origin (data not shown).

Because a more prolonged marrow recovery period and GVHD are associated with neutropenia in BMT subjects versus PBSCT patients, baseline characteristics and outcome measures between BMT and PBSCT subjects were compared (Table III). There was lower mean subject percent radiographic crestal alveolar bone loss and a significantly higher mortality rate in BMT subjects than in PBSCT subjects. Separate correlation analyses between these 2 treatment groups (BMT and PBSCT) demonstrated no association between mean subject percent radiographic crestal alveolar bone loss and microorganisms originating from periodontal, oral, or any site, as well as no association between mean subject percent radiographic crestal alveolar bone loss and 100-day post–HSCT mortality.

DISCUSSION

Currently, prechemotherapy and pre–HSCT recommendations include dental evaluation to identify and to treat potential oral sources of infection that might cause complications during immunosuppressive stages.[10,32] The dental community treating these patients has a broad interpretation of what constitutes a potential source of infection because few studies have examined oral disease and its treatment as a risk factor for HSCT outcome. Pretransplant dental care varies from very conservative management in which only abscessed teeth are removed to more aggressive treatment that includes removing asymptomatic teeth with significant alveolar bone loss.

We examined chronic periodontal disease as risk factor for septicemia in a patient group who were severely immunocompromised. The majority of patients received myeloablative HSCT therapy for hematologic malignancies, and all patients experienced a period of neutropenia of more than 10 days after transplantation. The high incidence of septicemia (64%) in our study population demonstrates their high susceptibility to infection. In addition, there were incidents of septicemia from bacteria typically found in the periodontal crevice or oral cavity, and many patients had poor periodontal health during the transplantation. Therefore, the cohort studied was potentially at risk for complications of periodontal or oral sepsis.

Although Schei ruler measurement does not reflect the presence or absence of active disease, it is an indirect assessment of the cumulative effects of periodontal disease.[24-31] It was used in previous studies to determine associations of periodontal disease with smoking,[25] cardiovascular disease,[28] peripheral vascular disease,[29] death from all causes,[31] with similar criteria for determination of clinical significant subject occurrence of periodontitis (mean subject radiographic crestal alveolar bone loss of 20% or greater) as was used in the present study. An earlier report using the Schei ruler showed a positive correlation between periodontal disease and age[33]; our data support this finding, because we also obtained a correlation between radiographic alveolar bone loss and age ($R = 0.49$, $P = .0001$). Indexes of periodontal disease such as probing depths were not uniformly recorded for all patients in the present study because some had neutropenia or thrombocytopenia when they presented for dental ex-

Table III. Baseline and outcome variables between BMT and PBSCT recipients

Variables	*BMT (n = 20)*	*PBSCT (n = 57)*	P *value*
Age (y ± SD)	34.2 ± 11.0	38.7 ± 12.1	0.14
Alveolar bone loss (% ± SD)	9.1 ± 5.9	13.7 ± 7.3	0.01*
Teeth extracted pre-HSCT	6 (30)†	26 (57)	.29
Periodontal microorganisms	5 (25)	15 (26)	.91
Oral microorganisms	6 (30)	17 (30)	.99
Any microorganism	16 (80)	33 (58)	.08
100-day mortality	10 (50)	11 (19)	.008*

*Significant at $P < .05$.
†Number and percentage (%) of patients in each category.

amination. Thus, our study examined cumulative periodontal disease rather than current periodontal status of patients. Many patients enrolled in the NIH protocols were referred from countries where dental care is not adequate, and most had no history of periodontal therapy other than extractions. However, 76.6% of the subjects had a simple dental prophylaxis before transplant, but additional extensive procedures such as scaling and root planing were not feasible. Therefore, it is likely that several patients with advanced bone loss had active periodontal disease, but this could not be established conclusively.

The rationale for examining the association between radiographic crestal alveolar bone loss and incidence of positive blood cultures in 3 different ways arose from previous studies demonstrating that periodontal and oral flora change during prophylactic antibiotic therapy.[10,15] These studies suggest that subgingival sites may yield a markedly different microbiota in the period immediately after HCST.[10,15] Therefore, we tested the data for 3 different associations: (1) mean subject percent radiographic crestal alveolar bone loss and the occurrence of blood cultures yielding microorganisms typically isolated from subgingival periodontal sites, (2) mean subject percent radiographic crestal alveolar bone loss and the occurrence of blood cultures containing microorganisms typically isolated from supragingival oral sites, and (3) mean subject percent radiographic crestal alveolar bone loss and the occurrence of any positive blood culture irrespective of its microbiologic composition. Interestingly, no statistically significant associations were found between radiographic periodontal status of the study subjects and the occurrence of septicemia-associated positive blood cultures. Patients with high amounts of crestal alveolar bone loss (mean, 20% or greater per subject) did not have a higher frequency of positive blood cultures and did not experience an increased risk of death in the first 100 days after transplant (although 2 of 21 patients who did not survive the first 100 days after transplant had radiographic crestal alveolar bone loss of 20% or greater). Our findings contrast with conclusions of others[13] who reviewed 38 cases retrospectively and deduced that oral infections were associated with febrile state and increased morbidity in patients with acute nonlymphocytic leukemia. In their report, 12 of the patients had oral infections, 8 of which were periodontal infections, but no statistical analyses or control group were provided. Moreover, no criteria were disclosed as to how they identified and classified infections of periodontal origin. A more recent prospective study also reported that the presence of chronic dental disease during chemotherapy did not affect outcome of cancer therapy.[34] However, because the study categorized the presence of probing depths of greater than 6 mm as *acute dental disease*, in contrast to our measurement of radiographic crestal alveolar bone loss, it is difficult to directly compare their data to the present study findings.

It is noteworthy that BMT and PBSCT patients exhibited differences in baseline characteristics and treatment outcomes. The lower radiographic crestal alveolar bone loss in BMT patients may be related to either better baseline periodontal health status or the removal of more teeth with advanced periodontal disease before HSCT, which would serve to reduce the measured radiographic values for crestal alveolar bone loss. The latter possibility is unlikely because only 30% of BMT patients as compared to 46% of PBSCT patients underwent 1 or more tooth extractions in the immediate time period before HSCT. However, it remains possible that more extractions of periodontally involved teeth may have been performed earlier in the BMT group before their enrollment in the various NIH treatment protocols.

Dental evaluation and treatment before chemotherapy and HSCT are still recommended as standard of care. Periapical pathologic condition should be treated because it is a risk factor for acquisition of viridans streptococcus bacteremia after transplant.[35] Before transplant therapy, patients should be given careful

instructions about the care of their mouth during chemotherapy and neutropenia. Severity and duration of oral mucositis immediately after transplant can be reduced by frequent oral hygiene procedures during periods of neutropenia.[36] Other oral problems such as deep caries should be treated before periods of prolonged immunosuppression, when elective dental treatment can place patients at risk.

The limitations of the present study must be noted. It represents a retrospective analysis of a relatively small sample of patients with mean radiographic crestal alveolar bone loss of 20% or greater, and 15% of the patients did not have prophylactic oral hygiene before HSCT, so additional studies are needed to confirm these preliminary findings. Although radiographs provide a record of cumulative effects of periodontitis,[33] cross-sectional evaluations of panoramic radiographs with a modified Schei ruler provide only indirect measures of periodontal status and do not assess the extent of gingival tissue inflammation, acute periodontal conditions, or periodontitis disease activity. Differences were noted in some baseline characteristics and treatment outcome measures between patients who received BMT and PBSCT. However, analysis of these 2 groups did not demonstrate a relationship between radiographic crestal alveolar bone loss and septicemia or 100-day mortality. Because fewer patients in the BMT group demonstrated compromised periodontal health (only 1 patient exhibited mean radiographic crestal alveolar bone loss of 20% or greater), no conclusions can be drawn about any potential association in this group between their periodontal status and the occurrence of post-HSCT septicemia. Although our overall findings do not support the need for prophylactic removal of teeth with marked radiographic alveolar bone loss before HSCT, a prospective, randomized controlled clinical trial would better address many unanswered questions about the presence of oral diseases and the potential risks they pose to HSCT recipients. Such a trial should include the effects of mucositis in addition to periodontal disease on common transplantation outcomes such as septicemia and GVHD.

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